

DISCUSSION OF THE CLAIMS

Claims 1-20 are pending in the present application. Claims 5-8 are presently withdrawn from active prosecution. Claims 19 and 20 are new claims. Support for new Claims 19 and 20 is found in the paragraph bridging pages 14 and 15 of the specification. Independent Claim 1 is amended to recite particular conditions under which the compound of formula (IV) is treated with a base to form the compound of formula (V). Support for the amendment to Claim 1 is found in the paragraph bridging pages 14 and 15.

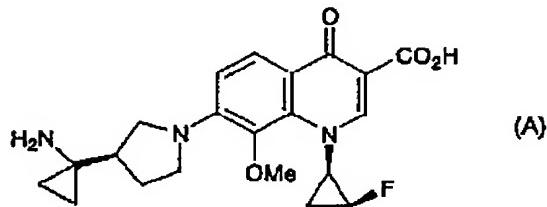
No new matter is added.

REMARKS

The present Supplemental Amendment is substantially the same as the amendment filed on October 6, 2010 with the following exceptions: (1) the reaction schemes presented in the Remarks are presented with greater definition, and (2) the reaction scheme on page 9 below is changed with respect to the starting materials and products for Reference Examples 1 and 2. Where the October 6, 2010 Amendment identified methoxy (-OMe) benzoic acid starting materials and products, the reaction scheme below correctly identifies the methyl (-Me) benzoic acid derivatives.

The presently claimed method includes a step in which a compound of formula (IV) is treated with potassium carbonate in DMF. The product of this reaction is a compound of formula (V). As shown in Example 3 of the present specification, it is possible to isolate the product formed by ring closure of compound (IV) in a yield of 76% based on the benzoic acid starting material. The yield demonstrated in Example 3 of the specification is desirably high from the perspective of industrial processes for making pharmaceutical compounds.

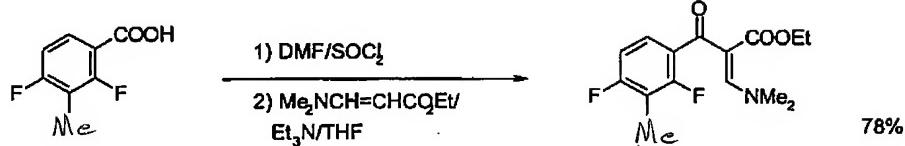
Applicants draw the Office's attention to co-pending application 11/644,901. The '901 application describes a quinolon compound of the following formula (A). The compound of formula (A), in one embodiment of the present invention, may be formed in the method of present Claim 18.



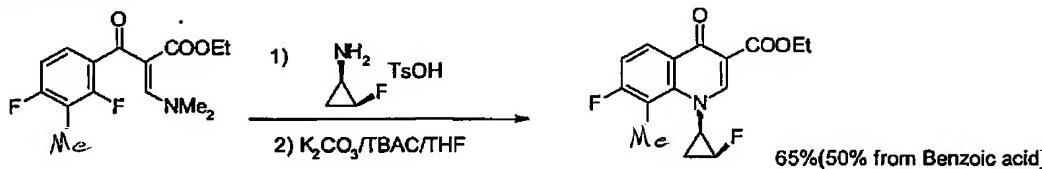
The examples of the '901 application are probative of the patentability of the presently claimed invention. Applicants draw the Office's attention to Reference Examples 1

and 2 of the '901 application. The chemical changes that are caused by Reference Examples 1 and 2 are shown below schematically:

Reference Example 1



Reference Example 2

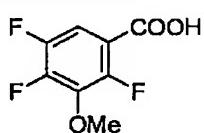


Reference Example 2 describes a ring closure reaction in which a fluorinated cyclopropylamine is reacted with a dimethylamino intermediate to form a quinolone compound. The reaction of Reference Example 2 of the '901 application is carried out in THF solvent and provides a 50% yield based on the benzoic acid starting material. As already mentioned above, the presently claimed invention includes a ring closure step which is carried out in a DMF solvent using a potassium carbonate base to provide the same ring closure product as formed in Reference Example 2 of the '901 application but in a substantially higher yield (i.e., 76% from the benzoic acid starting material in the present application in comparison to 50% from the benzoic acid starting material in the co-pending '901 application).

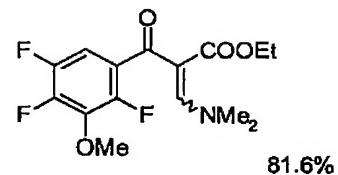
Applicants further draw the Office's attention to U.S. Patent No. 6,900,225. The '225 patent discloses one or more examples which are probative of the patentability of the presently claimed invention. The '225 patent describes the synthetic strategy shown schematically below. The product of the reaction of Reference Example 2 is obtained in a yield of 65% based on the benzoic acid starting material.

US Pat. No. 6,900,225
Reference Example 1 to 3

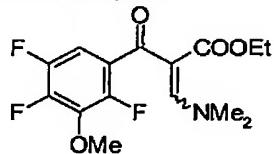
Reference Example 1



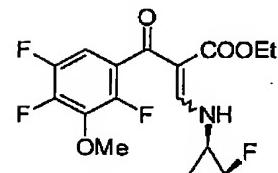
1) DMF/SOCl₂
2) Me₂NCH=CHCO₂Et/
Et₃N/THF



Reference Example 2

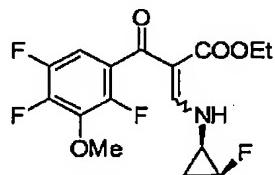


1) TsOH
2) Et₃N/CH₂Cl₂

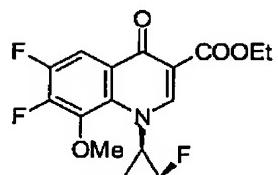


97.7%

Reference Example 3



K₂CO₃/DMF



81.8%

Like Reference Example 2 of the '901 application described above and like the treatment of the compound of formula (IV) with potassium carbonate in DMF to form the product of formula (V) of the present claims, the reaction of Reference Example 3 of the '225 patent is a ring closure. The respective ring closure reactions are nucleophilic displacement reactions on a 2-position of a benzene ring.

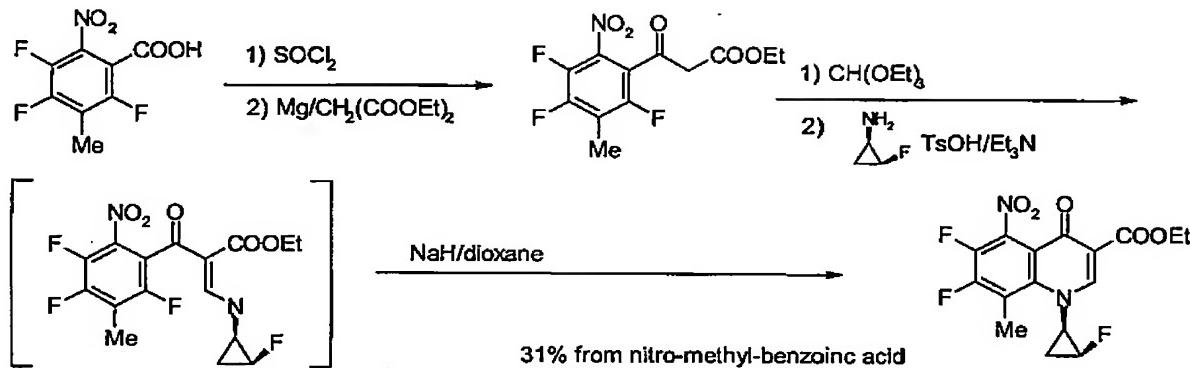
A comparison of the relative yields obtained from Reference Example 3 of the '225 patent and Example 3 of the present specification is probative as a showing of non-obviousness of the presently claimed invention. As is readily evident from a comparison of Example 3 above and Reference Example 3 of the '225 patent, the respective reactions are similar but begin from a different starting material. While the core carbon chain is the same between Example 3 and Reference Example 3, the '225 patent includes a starting material that is substituted on the benzene ring with 3 fluorine atoms whereas that of inventive Example 3 of the present specification is substituted with 2 fluorine atoms.

Those of skill in the art readily recognize that fluorine atoms are highly electrophilic, e.g., electron-withdrawing. Because the benzene ring of the starting material of the ‘225 reaction is substituted with more fluorine atoms than the benzene ring of present inventive examples, the electron density of the ‘225 benzene ring necessarily will be lower. Lower electron density corresponds with a lower electron density at the 2-position of the benzene ring where nucleophilic displacement occurs. A lower degree of electron density at the carbon atom of the 2-position functions to favor nucleophilic displacement in comparison with the nucleophilic displacement that occurs in inventive Example 3 wherein the carbon atom at the 2-position of the benzene ring has a relatively greater degree of electron density and is thus more resistant to nucleophilic displacement.

Notwithstanding the substantial advantage the compound of Reference Example 3 of the ‘225 patent has over Example 3 of the present specification, the relative yield obtained in inventive Example 3 is improved in comparison to the yield obtained for Reference Example 3 of the ‘225 patent. *Nothing in the art of record discloses or suggests that substantially improved ring closure yield can be obtained by carrying out the ring closure reaction of inventive Example 3 using DMF as a solvent and potassium carbonate as a base.*

U.S. Patent No. 5,849,757 discloses further reference examples that are probative of the non-obviousness of the presently claimed invention. Like the ring closure step recited in present Claim 1, Reference Examples 1-3 of the ‘757 patent describe the use of a DMF solvent.

US Pat. No. 5,849,757
Reference Example H-6 to H-7



The starting material on which the ring closure reaction of the '757 patent is carried out is substituted with three fluorine atoms (like the starting material of the Reference Examples of the '225) and is further substituted with a nitro group (i.e., -NO₂). Nitro groups like fluorine atoms are electron withdrawing substituents when present on a benzene ring. The carbon atom at the 2-position of the benzene ring of the '757 reaction is thus even further electron deficient relative to the corresponding carbon atom of the starting material described in inventive Example 3 of the present specification. One may expect that such electron deficiency would result in further improvements in yield for the ring closure reaction when carried out in the presence of DMF, the opposite is shown in the '757 patent. In fact, carrying out the '757 ring closure provides a yield of only 31% from the benzoic acid starting material. The reaction scheme is shown schematically above for convenience.

Applicants submit that the discussion above demonstrates the non-obviousness of the presently claimed invention, where one of ordinary skill in the art may expect poor yield of the ring closure step, Applicants have demonstrated that carrying out this step with potassium carbonate in DMF solvent provides unexpectedly high yields in comparison to the yields of analogous ring closure reactions carried out on similar starting materials having a greater degree of electron deficiency at the benzene atom.

In view of the discussion above, Applicants request withdrawal of the rejection and the allowance of all now-pending claims.

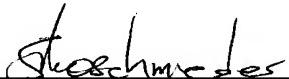
Respectfully submitted,

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